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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.

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EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1644	13

DATE MAILED: 08/14/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 5/24/01

☑ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 21-40 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 21-40 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

DETAILED ACTION

1. Applicant's amendment, filed 5/29/01 (Paper No. 10), is acknowledged.
Claims 1 and 16-20 have been canceled. Claims 2-15 have been canceled previously.

Claims 21-40 have been added.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 5/29/01 (Paper No. 10).
The rejections of record can be found in the previous Office Action (Paper No. 9).

3. Claims 21, 23-25, 29-31 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of Immunosuppressive drugs such as costimulatory molecule-specific inhibitors can be species- and model-dependent, it is not clear that reliance on the experimental observations with the use of certain CD28:B7-specific inhibitors in certain in vitro and in vivo settings accurately reflects the relative efficacy of the claimed therapeutic strategy to treat any autoimmune condition with B7-specific antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 5/29/01 (Paper No. 10), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant argues in conjunction with U.S. Patent No. 5,885,579 that ligands to B7 may be used in therapeutic methods wherein the inhibition of the interaction of a B7 antigen with CD28 is therapeutically desirable.
In contrast to applicant's assertions, the examiner is not raising doubts about the validity of a U.S. Patent.

While applicant focuses on the validity of in vitro assays for the efficacy of potential in vivo immunosuppressants; applicant is reminded that the claimed methods are drawn to treating autoimmune disorders with therapeutically effective amounts of B7.1- / CD80-specific antibodies.

Applicant argues in conjunction with U.S. Patent No. 6,162,432 that methods of treating skin disease including psoriasis with antibodies that inhibit LFA-3/CD2 interactions and other patents drawn to treating autoimmune diseases have been based on the ability to inhibit T cell activation and/or proliferation.

Applicant traverses the reliance upon Blazar et al, Perrin et al. And Daikh et al. To establish the problems and unpredictability of using B7-specific antibodies to treat autoimmune disorders and other diseases.

Applicant agues that Liu et al. (Digestive disease Week, May 21-24, 2000; #A583) supports the ability of anti-B7.1 antibodies, in contrast to anti-CTLA-4 and anti-B7.2 antibodies, to treat autoimmune responses in an animal model of colitis.

These observations by Liu et al. Are consistent with the differences between targeting different members of the CD28-B7 pathway in the treatment of different autoimmune diseases.

The following of record is reiterated for applicant's convenience

Blazar et al. (J. Immunol. 157: 3250-3259, 1996) disclose that anti-CD80 or anti-CD86 antibodies were ineffective in preventing T cell CD8-mediated GVHD lethality; that each antibodies was partially effective in CD4-mediated GVHD lethality and that the combination of anti-CD80 and anti-CD86 antibodies were effective in preventing GVHD lethality in murine experimental models (see entire document, including the Abstract)

Perrin et al. (J. Neuroimmunol. 65: 31-39,1996) disclose that in contrast to the effective treatment of disease with CTLA-4 Ig; anti-CD80 (B7-1) attenuated the first clinical disease episode but not the relapse, anti-CD86 (B7-2) had no significant effect on the course of disease, and the combined treatment with anti-CD80 plus anti-CD86 resulted in the exacerbation of disease (see entire document). It is also noted that CTLA-4 Ig had a marked but incomplete therapeutic effect in the EAE model.

In addition, Yi-qun et al. (Intl. Immunol. 8: 37-44, 1996) disclose that their findings have a number of important implications for therapeutic approaches (see entire document, particularly Discussion, last paragraph). It is clear that inhibition of T cell response to soluble antigens will require the blocking of both B7-2 and B7-1 to be effective. More, important it is unlikely that ongoing T cell response will be susceptible to inhibition by anti-B7 reagents, for example in autoimmune diseases.

Daikh et al. (J. Leukoc. Biol. 62: 156-162, 1997) disclose that the role of CD28-B7 interactions are complex in autoimmune diseases and that B7-1-specific antibodies can exacerbate disease in an experimental model of diabetes (see pages 159-160, Effects of Selective Blockade of B7-1 of B7-2 on Autoimmunity).

Also, it is noted that targeting colitis with B7-1-specific antibodies, does not appear in the specification as-filed.

As pointed out previously, immunosuppression and inhibition of immune disorders are much easier to achieve under controlled in vitro conditions that experienced in the human immunoregulatory diseases targeted by the claimed invention. Here, the reliance upon observations wherein the B7-CD28 inhibitor antagonists are administered at the same time as initial stimulus or insult in experimental models are acknowledged. Even though subsequent secondary responses may be affected, such observations still rely upon inhibiting activation of B7-CD28 interactions at the onset or initiation of experiencing the antigen or stimulus and not upon experiencing an ongoing responses wherein secondary responses or antigen experienced lymphocytes are already in place. In contrast, the claimed methods encompass using B7-1 specific antibodies to treat autoimmune diseases wherein the diagnosis of such diseases occur after antigen priming has occurred.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective costimulatory-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting any autoimmunity with B7-1-specific antibodies alone.

Applicant's arguments have not been found persuasive.

It is noted that treating psoriasis with B7-1-specific antibodies is considered enabled.
See Gottlieb et al., Journal of Investigative Dermatology 114(4): 840, (2000); Abstract # 546.

5. Claims 21-40: It is apparent that the 16C10, 7C10, 20C9 and 7B6 antibodies are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the appropriate cell lines / hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

Applicant's statements, filed 5/29/01 (Paper No. 10), concerning that the independent claim now provides that the recited antibodies possess specific primatized variable heavy and light sequences and, in turn, do not require deposit as the requisite sequences are provided are acknowledged.

However, these arguments have been fully considered but are not found convincing essentially for the reasons of record.

It is noted that the sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin. Note that satisfaction for the biological deposit of the specific 16C10, 7C10, 20C9 and 7B6 antibodies require the disclosure and recitation of its entire amino acid sequences and not based upon partial sequences. Here, the sequences recited in independent claim are limited to the variable chains of said antibodies and not their entire sequences.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Applicant's arguments are not found persuasive.

6. Claims 21-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21-40 are indefinite in the recitation of "16C10, 7C10, 20C9 and 7B6" because their characteristics are not known. The use of "16C10, 7C10 and 7B6" monoclonal antibodies as the sole means of identifying the claimed antibodies renders the claim indefinite because "16C10, 7C10, 20C9 and 7B6" are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct hybridomas / cell lines.

Applicant's statements, including the reliance on recited sequences, filed 5/29/01 (Paper No. 10), have been fully considered but are not found convincing essentially for the reasons of record.

Also, as pointed out above it is noted that the sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin. Note that satisfaction for the biological deposit of the specific 16C10, 7C10 and 7B6 antibodies require the disclosure and recitation of its entire amino acid sequences and not based upon partial sequences. Here, the sequences recited in independent claim are limited to the variable chains of said antibodies and not their entire sequences.

Therefore, in turn, the metes and bounds of the laboratory designations of "16C10, 7C10 and 7B6" are ill-defined and ambiguous.

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

7. Claims 21-23, 26, 29, 30, 32, 35, 38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Linsley et al. (U.S. Patent No. 5,885,579) and de Boer et al. (U.S. Patent No. 5,747,034) in view of Nickoloff et al. (Blood 83: 2580-2586, 1994) and in view of art-known procedures and motivation to generate recombinant antibodies (e.g. humanized, chimeric or primatized) for diagnostic and therapeutic regimens as acknowledged on pages 13-16 and 22-33 of the specification (e.g. Newman et al. Biotechnology,10 ; 1455-1460 1992)

The instant claims are drawn to methods of treating psoriasis with B7-1-specific antibodies having the epitopic specificity of 16C10, 7C10 and 7B6; which appear to be antibodies that specifically bind to B7.1 (CD80) and which inhibit the binding of B7.1 antigen to CD28, but which antibodies do not inhibit the binding of B7.1 to CTLA-4.

Linsley et al. teach the use of B7-specific antibodies to inhibit CD28-B7 interactions (columns 18-19, overlapping paragraph) in order to treat autoimmune diseases such as psoriasis (column 9, line 12) (see entire document).

Linsley et al. teach the role of the B7 molecules as well as CTLA-4 and CD28 in cell signaling and various molecules including antibodies to block their functions (see entire document).

Also, Linsley et al. teach anti-B7 antibodies may be used to bind to B7 to inhibit interactions of CD28-positive "or" CTLA-positive T cells with B7 positive cells (see column 15, paragraph 7).

By teaching the inhibition of CD28 or CTLA interactions in the alternative; one of ordinary skill in the art at the time the invention was made would have had an expectation of success in generating B7.1-specific antibodies that could block B7:CD28 interactions OR B7:CTLA-4 interactions.

De Boer et al. teach methods of treating autoimmune diseases (column 14; Section IV and Summary of the Invention) with human B71-specific antibodies, including B7-24, that bind an epitope that differs from the prior art B7-specific antibodies, wherein the specificity inhibits CD28 binding and T cell activation but differs from a CTLA-4 binding epitope (see entire document; including column 5, lines 49-65; column 6, lines 24-41; column 25, lines 28-30; columns 27-28, Example 14). In addition, this reference teaches various recombinant forms of said antibodies and pharmaceutical compositions thereof (columns 7-16).

Also, it is noted that de Boer et al. indicate that while the B7 molecules as well as CTLA-4 and CD28 are involved in cell interactions and signaling; there are distinct differences in their properties as well as the binding and inhibitory properties of various molecules. See Detailed Description of the Invention, including columns 5-6. Therefore, de Boer clearly recognizes differences between CD28 and CTLA-4 as they apply to their interaction with B7 at the time the invention was made.

Linsley et al. differ from the claimed methods by not exemplifying the treatment of psoriasis with B7-1-specific antibodies.

Linsley et al. and De Boer et al. differ from the instant claims by not disclosing the art known use of primatized (as it differs from humanized) forms of recombinant antibodies and the particular 16C10, 7C10 and 7B6 B7-1 specificities per se.

In agreement with the specification, it was well known in the art at the time the invention was made to chimerize/primatize/humanize antibodies to have readily available reagents suitable for human diagnosis and therapy and their respective use in primate models. For example, Newman et al. teach the protocols of primatizing antibodies including the use of computer analysis of the instant invention (see entire document). The recombinant techniques and computer analyses of immunoglobulin sequences as taught by the references would have resulted in the same or very nearly the same characteristics of the instant claims since both the references and instant invention use the same techniques, the same antibody specificities and the same goals. The ordinary artisan would have achieved either the same or functional equivalents of the instant B7.1-specific antibodies, as such properties are taught by De Boer et al.. Also, note that the claims do not require that one generates the exact same antibody as the instantly disclosed 7C10, 7B6 and 16C10 antibodies, but rather isolates an antibody that has the same functional characteristics as said antibodies.

The claimed functional limitations would have been expected properties of the referenced B7-specific inhibitory antibodies.

As pointed out previously, Nickoloff et al. teach the expression of B7-1 on lymphocytes in the chronic skin disorder of psoriasis, which, in turn, contributes to the ongoing T cell proliferation that occurs in the skin of patients afflicted by these disorders (see entire document, including the Discussion).

Given the clear teachings of Linsley et al. to use B7-specific antibodies to inhibit CD28-B7 interactions to treat an autoimmune disease such as psoriasis as well as the teachings of de Boer to treat autoimmune disease with B7-1-specific antibodies and given the teachings of Nickoloff et al. of the particular expression of B7-1 on T cells in the skin of psoriatic patients; the ordinary artisan would have been motivated to target B7-1 expressing cells in psoriasis.

One of ordinary skill in the art at the time the invention was made would have been motivated to select recombinant B7.1-specific antibodies, including primatized antibodies, to treat an autoimmune disease such as psoriasis.

It would have been obvious to one of ordinary skill in the art to target B7-1-expressing cells with B7-1-specific antibodies alone or in combination with other immunosuppressives in order to inhibit in appropriate immune responses, including those associated with psoriasis.

Given that CD28/CTLA-4 were known to structurally and functionally distinct; the ordinary artisan would have had an expectation of success in generating antibodies which inhibit B7-CD28 binding and not B7-CTLA-4 binding at the time the invention was made; thereby providing an expectation of success in generating anti-B7.1 antibodies that have the same epitopic specificity as 16C10, 7C10 and 7B6.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Applicant's arguments, filed 5/29/01 (Paper No. 10), have been fully considered but are not found convincing essentially for the reasons of record and those set forth herein.

Applicant arguments concerning B7-specific antibodies and their fine specificities are addressed in the rejection set forth above in Section 8.

Given the clear prior art teachings set forth above in Section concerning that Linsley et al. teach to target psoriasis and Nickoloff et al. teach the expression of B7-1 on lymphocytes in the chronic skin disorder of psoriasis, which, in turn, contributes to the ongoing T cell proliferation that occurs in the skin of patients afflicted by these disorders; applicant's arguments in conjunction with Liu et al. Abstract are not found persuasive as they appear to read on a lack of expectation of success in the prior art.

Applicant's arguments are not found persuasive.

10. As pointed out previously, applicant's submitted claims drawn to methods employing the 7C10, 7B6 and 16C10 specific antibodies appear free of the prior art.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
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August 8, 2001